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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/728,051 | CAPLAN, MICHAEL J. | |
| | Examiner | Art Unit | |
| | Phuong Huynh | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11/7/05; 12/27/05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *34-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 34-45 are pending.

2. In view of the amendment filed 11/7/05, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 34-45 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising dead *E. coli.* containing therein at least one peanut allergen encoded by the nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 2 and 3 (See page 33 of the specification), **does not** reasonably provide enablement for (1) any pharmaceutical composition comprising dead *E. coli.* containing therein at least one of any "modified peanut allergen whose amino acid sequence differs from that of wild-type" peanut allergen Ara h1, Ara h2 and Ara h3 as set forth in claims 34-37 and 39-45, and (2) any pharmaceutical composition comprising dead E. coli containing therein at least one modified peanut allergen whose amino acid sequence differs from that of a wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen, wherein the wild-tvpe peanut allergen is an Ara h 1, Ara h 2 or Ara h 3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO:1. SEO ID NO:2. or SEO ID NO:3 wherein the modified peanut allergen differs from the sequence of the wild-type peanut allergen by any one or more amino acid "deletions", "substitutions", or "additions" within any IgE binding site of any wild-type peanut allergen for a vaccine or a method of treating allergy in a subject susceptible to an anaphylactic allergic response to peanut. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope

of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only composition comprising heat killed *E coli.* containing therein at least one unmodified recombinant peanut allergen Ara h1 encoded by SEQ ID NO: 1, a recombinant peanut allergen Ara h2 encoded by SEQ ID NO: 2 or a recombinant peanut Ara h3 encoded by SEQ ID NO: 3 and a pharmaceutical acceptable carrier (page 31 of the specification). The specification further discloses a method of immunizing mice with said bacteria that produce said peanut allergens (page 34 of the specification). However, mice that have been immunized with the heat killed bacteria that makes Ara h1 fail to produce any detectable levels of Ara h1 specific IgG which is critical for converting a Th2 immune response to a Th1 immune response as a method of treating peanut allergy in a subject (See page 34 of specification). Furthermore, mice immunized with *E. coli* that makes Ara h2 produce high levels of IgG1 (indicative of Th2 immune response) and IgG2a (indicative of Th-1 type immune response), which again fails to modulate the host immune response to peanut allergen Ara h2 toward Th1 type response. Finally, mice immunized with *E. coli* that makes Ara h3 produce high levels of IgG2a (indicative of Th-1 type immune response) and low levels of IgG1 (indicative of Th2 immune response).

The specification does not teach how to make and use any composition comprising dead *E coli* containing any and all "modified peanut allergen" whose amino acid sequence differs from the sequence of the wild-type peanut allergen such as Ara h1 encoded by SEQ ID NO: 1, Ara h2 encoded by SEQ ID NO: 2 and Ara h3 encoded by SEQ ID NO: 3 by one or more amino acid deletions, substitution, additions within which IgE binding site of said wild-type peanut allergen such that the allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen. There is insufficient guidance as to which amino acids corresponds to which IgE binding site to be modified by deletion, addition, substitution and combination thereof in Ara h1, Ara h2 and Ara h3 encoded by nucleotides within the full length nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3 that can be deleted, substituted, added or combination thereof such that the resulting the modified peanut allergen has a reduced ability to bind to or cross-linked IgE in the claimed pharmaceutical composition for treating peanut allergy.

Further, there is a lack of guidance as to the structure of the modified peanut allergen without the amino acid sequence, the corresponding nucleic acid sequence.

Burks et al (Eur. J Biochem 245(2): 334-9, April 1997; PTO 1449) teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al* (Arch Biochem Biophys 342(2): 244-53, June 1997; PTO 1449) teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley *et al* also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Given the unlimited number of modified peanut allergen, it is unpredictable which undisclosed modified peanut allergen in the claimed composition is effective for treating peanut allergy. Without the amino acid sequence of the modified peanut allergen, the cDNA encoding the corresponding modified allergen, one of skilled in the art cannot make the recombinant modified peanut allergen in E coli, much less for use in treatment of peanut allergy.

Chatel et al teach various factors such as the nature of the allergen, the mouse strain, the recombinant protein expressed influence the immune response to peanut allergen (see abstract, in particular). Chatel et al teach immune responses to proteins are known to be highly dependent on the nature of the allergen (see page 646, col. 1, first paragraph, in particular). Chatel et al teach immune response are also depends on the mouse strain (see page 646, col. 1, fourth paragraph, in particular).

Gottieb et al teach the immune system of mice is also quite different from that of man (see page 894, col. 3, in particular). Given the unlimited number of modified peanut allergens

expressed in the dead E coli in the claimed composition, there is insufficient in vivo working example demonstrating the claimed composition is effective for treating peanut allergy.

Finally, immunizing mice with heat killed *E. coli* producing three different recombinant unmodified peanut allergens results in three different outcomes (see page 34 of instant specification). In *re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 11/7/05 have been fully considered but are not found persuasive.

Applicants' position is that first, microorganisms such as *E. coli* tend to produce Th1-type (i.e., non-allergic) immune reactions in individuals. In contrast, allergens such as the peanut allergens Ara h 1, 2 and 3 tend to produce Th2-type (i.e., allergic) immune reactions. Th1-type immune reactions and Th2 type immune reactions are mutually inhibitory. One aspect of the present invention is the recognition that, by administering allergens in the context of microorganisms such as E. coli, it might be possible to cause a recipient individual to mount a Th1-type immune reaction to the administered allergen, and therefore to suppress any Th2-type reaction to that allergen (see specification, for example, (00411). The specification describes the administration of *E. coli* cells that contain the peanut allergens Ara h 1, 2 or 3 to mice. According to the Examples, high levels of IgG2a (indicative of a Th1-type response) were observed for both Ara h 2 and Ara h 3. High levels of IgG1 (indicative of a Th2-type response) were also observed for Ara h 2. Antibody levels were not high enough for Ara h 1 to detect whether Th2-type or Th1-type responses were occurring. Thus, the specification exemplifies initiation of a Th1-type immune reaction to peanut allergens Ara h 2 and Ara h 3 expressed in E. coli. It is true that evidence of a Th2-type reaction was also observed for Ara h 2, but that was explained as resulting

from released protein which, obviously, would be expected to induce a strong Th2 response. Second, The claimed compositions comprise dead E. coli cells that contain modified peanut allergens with reduced IgE binding. The examiner argues that it would require undue experimentation to make any suitably modified peanut allergens because the selection of mutations) would be too unpredictable. To support this argument, the examiner points to applicant's own peptide mutational studies with Ara h 1, Burks et al.) and Ara h 2 (Stanley et a1). Specifically, the examiner jumps on the fact that some of the Ara h 1 and Ara h 2 mutations that applicant tested failed to reduce IgE binding or even increased IgE binding (see page 5 of Office Action). According to this examiner, these "'failures" render the mutational step so unpredictable that it would require undue experimentation to practice the claimed invention. In fact, as far as this examiner is concerned the mutational step is rendered so unpredictable by these "failures" that a skilled person would have been unable to make a suitably modified peanut allergen without actually being given "the amino acid sequence of the modified peanut allergen and the cDNA encoding the corresponding modified allergen" (see page 5 of Office Action). This argument is absurd for several reasons. First, it disregards the fact that Burks et al., Stanley et al. and the current application describe a vast number of Ara h 1, 2 and 3 mutations that did reduce IgE binding (e.g., see the numerous mutations that are listed in the Tables and Examples of .U.S. Serial No. 09/141,220 that is incorporated by reference in (0069). Thus, the present application explicitly enables the making of a significant number of species within the claimed genus. These "successes" would have weighed heavily against the "failures" that the examiner refers to - the level of predictability can only be assessed by considering both. The fact that the prior art and the current application demonstrate a frequency of "successes" that far outweighs the frequency of "failures" would have clearly indicated to a person of ordinary skill that the mutational step was far more predictable than the examiner suggests. Second, the examiner's argument does not take into account the nature and amount of experimentation that would actually be required to identify suitable mutations that are not explicitly described in the application. In particular, as set forth in Wands, when the starting materials are readily available and the experimentation is of a routine nature then the level of experimentation is not undue. This is true even if a significant amount of experimentation would be required.

In response, the claimed encompassed any pharmaceutical composition comprising dead *E coli* containing therein any modified peanut allergen from Ara h1, Ara h2 and Ara h3 whose

amino acid sequence differs from that of wild-type peanut that occurs in nature such that the modified peanut allergen has reduced ability to bind or cross-link IgE as compared to wild-type peanut allergen wherein the wild-type peanut allergen Ara h1 is encoded by nucleotide sequence of SEQ ID NO: 1, Ara h2 is encoded by nucleotide sequence of SEQ ID NO: 2 and Ara h3 is encoded by nucleotide sequence of SEQ ID NO: 3 as a vaccine for treating peanut allergy.

The specification at page 33 discloses a composition comprising dead *E. coli.* containing therein unmodified peanut allergen Ara h1, Ara h2 and Ara h2 encoded by the nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 2 and 3, respectively (See page 33 of the specification, references cited therein).

The specification does not teach any nucleic acid encoding any modified peanut allergen whose amino acid sequence differs from that of any wild-type peanut allergen that occurs in nature such that the modified peanut allergen has reduced ability to bind to or cross-link IgE as compared with wild-type peanut allergen Ara h1, Ara h2 and/or Ara h3, much less dead E coli containing therein any modified Ara h1, Ara h2 or Ara h3 as a pharmaceutical composition or vaccine for peanut allergy. As evidence by the teachings of Burks et al that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular). Likewise, Stanley *et al* (Arch Biochem Biophys 342(2): 244-53, June 1997; PTO 1449) teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley *et al* also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Given the unlimited number of modified peanut allergen, it is unpredictable which undisclosed modified peanut allergen in the claimed pharmaceutical composition is effective for treating peanut allergy. Without the amino acid sequence of the modified peanut allergen, the corresponding cDNA encoding the corresponding modified allergen, one of skilled in the art cannot make the recombinant modified peanut allergen in *E coli*, much less for use in treatment of peanut allergy or as a vaccine.

Chatel et al teach various factors such as the nature of the allergen, the mouse strain, the recombinant protein expressed influence the immune response to peanut allergen (see abstract, in particular). Chatel et al teach immune responses to proteins are known to be highly dependent on the nature of the allergen (see page 646, col. 1, first paragraph, in particular). Chatel et al teach immune response are also depends on the mouse strain (see page 646, col. 1, fourth paragraph, in particular). Given the unlimited number of modified peanut allergen, it is unpredictable which modified peanut allergen Ara h1, Ara h2 and Ara h3 has reduced ability to bind and cross-linked IgE upon expressed in the E coli and then rendered dead for a pharmaceutical composition. Until the structure of the modified peanut allergen Ara h1, Ara h2 and Ara h3, the corresponding nucleic acid encoding said modified peanut allergens have been taught, the specification as filed merely extends an invitation to one skilled in the art to come up with the structure of the modified peanut allergen Ara h1, Ara h2 and Ara h3 and then expressed in *E coli,* rendered said E coli dead by heat or chemical means as a pharmaceutical composition or vaccine for treating or preventing peanut allergy.

The specification describes the administration of *E. coli* cells that contain the unmodified peanut allergens Ara h 1, 2 or 3 to mice (see references therein on page 33 of specification). Even with the unmodified peanut allergen, mice that have been immunized with the heat killed bacteria that makes Ara h1 fail to produce any detectable levels of Ara h1 specific IgG which is critical for converting a Th2 immune response to a Th1 immune response as a method of treating peanut allergy in a subject (See page 34 of specification). Furthermore, mice immunized with *E. coli* that makes Ara h2 produce high levels of IgG1 (indicative of Th2 immune response) and IgG2a (indicative of Th-1 type immune response), which again fails to modulate the host immune response to peanut allergen Ara h2 toward Th1 type response. Finally, mice immunized with *E. coli* that makes Ara h3 produce high levels of IgG2a (indicative of Th-1 type immune response) and low levels of IgG1 (indicative of Th2 immune response). There is no disclosure of administering dead E. coli cells that contain any modified peanut allergens with reduced IgE binding, let alone the pharmaceutical comprising dead E. coli cells that contain modified peanut allergens with reduced IgE binding is effective as a vaccine for treating or preventing peanut allergy. Further, Chatel et al teach various factors such as the nature of the allergen, the mouse strain, the recombinant protein expressed influence the immune response to peanut allergen (see abstract, in particular). Chatel et al teach immune responses to proteins are known to be highly dependent on the nature of the allergen (see page 646, col. 1, first paragraph, in particular).

Chatel et al teach immune response are also depends on the mouse strain (see page 646, col. 1, fourth paragraph, in particular). Gottieb et al teach the immune system of mice is also quite different from that of man (see page 894, col. 3, in particular). Given the unlimited number of modified peanut allergens having one or more amino acid substitution, deletions or additions within any IgE binding site expressed in the dead *E coli* as a pharmaceutical composition, and the insufficient in vivo working example, accordingly, undue experimentation would be required for one skilled in the art to practice the claimed invention.

With respect to the argument of incorporation by reference to USSN 09/141,220 at page 7 of the remark, USSN 09/141,220 has not been issued as a patent and therefore information containing therein incorporated by reference is not available to the public.

5. Claims 34-45 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for (1) any pharmaceutical composition comprising dead *E. coli.* containing therein at least one of any "modified peanut allergen whose amino acid sequence differs from that of wild-type" peanut allergen Ara h1, Ara h2 and Ara h3 as set forth in claims 34-37 and 39-45, and (2) any pharmaceutical composition comprising dead E. coli containing therein at least one modified peanut allergen whose amino acid sequence differs from that of a wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen, wherein the wild-tvpe peanut allergen is an Ara h l, Ara h 2 or Ara h 3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO:1. SEO ID NO:2. or SEO ID NO:3, respectively wherein the modified peanut allergen differs from the sequence of the wild-type peanut allergen by any one or more amino acid "deletions", "substitutions", or "additions" within any IgE binding site of any wild-type peanut allergen as set forth in claim 38 for a vaccine or a method of treating allergy in a subject susceptible to an anaphylactic allergic response to peanut.

The specification discloses only a composition comprising heat killed *E coli.* containing therein at least one recombinant peanut allergen Ara h1 encoded by SEQ ID NO: 1, a recombinant peanut allergen Ara h2 encoded by SEQ ID NO: 2 or a recombinant peanut Ara h3

encoded by SEQ ID NO: 3 and a pharmaceutical acceptable carrier (page 31 of the specification). The specification further discloses a method of immunizing mice with said bacteria that produce said peanut allergens (page 34 of the specification). However, mice that have been immunized with the heat killed bacteria that makes Ara h1 fail to produce any detectable levels of Ara h1 specific IgG which is critical for converting a Th2 immune response to a Th1 immune response as a method of treating peanut allergy in a subject (See page 34 of specification). Furthermore, mice immunized with *E. coli* that makes Ara h2 produce high levels of IgG1 (indicative of Th2 immune response) and IgG2a (indicative of Th-1 type immune response), which again fails to modulate the host immune response to peanut allergen Ara h2 toward Th1 type response. Finally, mice immunized with *E. coli* that makes Ara h3 produce high levels of IgG2a (indicative of Th-1 type immune response) and low levels of IgG1 (indicative of Th2 immune response).

Other than the specific composition mentioned above, there is inadequate written description about the structure associated with function of the "modified peanut allergen" in the claimed composition without the amino acid sequence, the corresponding cDNA encoding said modified peanut allergen containing therein in the dead *E coli* of the claimed composition. Further, the specification has not described which one or more amino acids within which IgE binding sites of Ara h1 encoded by SEQ ID NO: 1, Ara h2 encoded by SEQ ID NO: 2 and Ara h3 encoded by SEQ ID NO: 3 to be deleted, substituted, added or combination thereof. Since the modified peanut allergen containing in the dead *E coli* of the claimed composition is not adequately described, it follows that the composition wherein the modified peanut allergen is located in the cytoplasm or the periplasm of the dead *E coli* are not adequately described. It also follows that the composition wherein the modified peanut allergen cannot be detected by any antibody binding without disrupting the dead E coli is not adequately described.

The specification discloses only dead E coli containing recombinant peanut allergen Ara h1 encoded by SEQ ID NO: 1, Ara h2 encoded by SEQ ID NO: 2 and Ara h3 encoded by SEQ ID NO: 3, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of modified peanut allergen containing in the dead *E coli* in the claimed composition to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 11/7/05 have been fully considered but are not found persuasive.

Applicants' position is that while compositions with *E. coli* containing modified peanut allergens were not reduced to practice these species were comprehensively described in the specification. Notably, the specification explicitly stated that modified peanut allergens were preferred alternatives to unmodified peanut allergens for use in inventive compositions (see (0069)). Indeed, as stated in the specification, modified peanut allergens with reduced IgE binding present a reduced risk of causing an allergic or anaphylactic response in individuals that are treated with vaccines containing the inventive compositions. The specification also provided a detailed description of the amino acid structures of a representative number of modified peanut allergens via incorporated application U.S. Serial No. 09/141,220 (see (00691). Thus, the specification specifically highlighted that substitutions at different positions, and with different amino acids, achieved the same results. Despite this extensive description, the examiner rejected the narrow claims on the ground that "without the amino acid sequence (and) the corresponding cDNA encoding said modified peanut allergen (...)" there is inadequate written description of "the structure associated with function of the modified peanut allergen" (see page 8 of Office Action). In essence, the examiner is taking the position that applicant is only (if at all) entitled to claim compositions that include the specifically modified peanut allergens for which amino acid sequences have been provided. This is clearly not the law nor should it be.

In response, the claimed encompassed any pharmaceutical composition comprising dead *E coli* containing therein any modified peanut allergen from Ara h1, Ara h2 and Ara h3 whose amino acid sequence differs from that of wild-type peanut that occurs in nature such that the modified peanut allergen has reduced ability to bind or cross-link IgE as compared to wild-type peanut allergen wherein the wild-type peanut allergen Ara h1 is encoded by nucleotide sequence of SEQ ID NO: 1, Ara h2 is encoded by nucleotide sequence of SEQ ID NO: 2 and Ara h3 is encoded by nucleotide sequence of SEQ ID NO: 3 as a vaccine to prevent peanut allergy (see summary of invention).

The specification at page 33 discloses a composition comprising dead *E. coli.* containing therein unmodified peanut allergen encoded by the nucleic acid sequence selected from the group

consisting of SEQ ID NO: 1, 2 and 3 (See page 33 of the specification) (see references cited therein).

The specification does not describe any nucleic acid encoding any modified peanut allergen whose amino acid sequence differs from that of any wild-type peanut allergen that occurs in nature such that the modified peanut allergen has reduced ability to bind to or cross-link IgE as compared with wild-type peanut allergen Ara h1, Ara h2 and/or Ara h3, much less dead E coli containing therein any modified Ara h1, Ara h2 or Ara h3 as a pharmaceutical composition or vaccine for peanut allergy. The specification does not describe any modified Ara h1, Ara h2 and/or Ara h3 contained in *E coli* as a pharmaceutical composition. As stated earlier, USSN 09/141,220 has not been issued as a patent and therefore information containing therein incorporated by reference is not available to the public. Until the structure of the modified peanut allergens with reduced IgE binding present in *E coli* has been described, the specification as filed merely ask one of skilled in the art to come up with the structure of the modified peanut allergen for the claimed pharmaceutical composition. The "one or more amino acid deletions, substitutions or additions" within the IgE binding of any wild-type peanut allergen such as Ara h1, Ara h2 and Ara h3 would have no resemblance to wild-type peanut encoded by SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3, respectively. Accordingly, the modified peanut allergen contained in *E coli* of the claimed pharmaceutical composition is not adequately described.

The specification discloses only dead *E coli* containing recombinant unmodified peanut allergen Ara h1 encoded by SEQ ID NO: 1, Ara h2 encoded by SEQ ID NO: 2 and Ara h3 encoded by SEQ ID NO: 3, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of "modified peanut allergen whose amino acid sequence differs from that of a wild-type peanut allergen that occurs in nature containing in the dead *E coli* in the claimed pharmaceutical composition to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

6. The following new grounds of rejections are necessitated by the amendment filed 11/7/05.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 34-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,888,799 (of record, March 1999, PTO 1449) in view of WO 99/38978 publication (of record, Aug 1999, PTO 1449) and Yeung et al (of record, J Immunology 161: 4146-4152, 1998; PTO 892).

The '799 patent teaches a composition comprising live bacteria such as *E. coli* K-12 containing therein any allergen and a pharmaceutically acceptable carrier to the mucosal immune system (See entire document, col. 2, line 25-34, col. 7, line 53, col. 9, lines 59-67, in particular). The reference microorganism such as *E. coli* K-12 have the advantages of (1) being avirulent (derivative of a pathogenic strain) and do not exchange genetic material with the pathogenic strains, (2) useful as delivery vehicle to stimulate the host cellular response such as the production of IgA in the secretory pathway with a concomitant stimulation of the humoral and cellular immune response (See column 2, lines 60-64, column 5, Table 1, in particular).

The claimed invention as recited in claim 34 differs from the teachings of the reference only in that the pharmaceutical composition comprising dead *E coli* containing therein at least one modified allergen whose amino acid sequence differs from that of a wild-type allergen that occurs in nature such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the non-modified allergen wherein the wild-type peanut allergen is Ara h1, Ara h2 or Ara h3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3 and a pharmaceutically acceptable carrier.

The claimed invention as recited in claim 35 differs from the teachings of the reference only in that the pharmaceutical composition comprising dead *E coli* wherein the wild-type peanut allergen is an Ara h1 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: 1.

The claimed invention as recited in claim 36 differs from the teachings of the reference only in that the composition comprising dead *E coli* wherein the wild-type peanut allergen is an Ara h2 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: 2.

The claimed invention as recited in claim 37 differs from the teachings of the reference only in that the composition comprising dead *E coli* wherein the wild-type peanut allergen is an Ara h3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: 3.

The claimed invention as recited in claim 38 differs from the reference from the teachings of the reference only in that the composition dead *E coli* containing therein modified allergen whose amino acid sequence differs from the sequence of wild-type allergen by one or more amino acid amino acid deletions, substitution, or addition within an IgE binding site of the wild-type peanut allergen.

The claimed invention as recited in claim 39 differs from the reference from the teachings of the reference only in that the composition dead *E coli* containing therein modified allergen lacks a portion of the wild-type allergen within said portion includes IgE binding site.

The WO 99/38978 publication teaches a composition comprising live *E coli* containing therein at least one peanut allergen such as Ara h1, Ara h2 and Ara h3 where the amino acids within each of the binding sites have been substituted such that the modified allergens have reduced IgE binding compared with the wild-type (see page 3, line 22-30, page 10, line 10-16, page 16, line 22-33, in particular). The reference further teaches a method comprising the steps of providing a composition comprising a modified allergen such as peanut protein Ara h1, Ara h2, Ara h3 or a portion thereof wherein the protein or portion thereof has at least one amino acid has been deleted or substituted such that the modified protein has a reduced ability to bind and crosslink IgE antibodies (See Abstract, page 19, reference SEQ ID NO: 2, 4 and 6, claims 14, 17-20, 23 and 36 of WO 99/38978 publication, in particular). The reference modified peanut allergen is expressed or produced in a recombinant host such as bacteria wherein the allergen is secreted into the periplasma space since the bacterial cells must be lysed in denaturing binding buffer (See claim 27 of WO 99/38978 publication, page 16, lines 30-32, in particular). The WO 99/38978 publication further teaches the critical amino acids within each of the IgE binding epitope of the peanut protein such as Ara h1, Ara h2 and Ara h3 that are important for IgE binding and substitution of a specific single amino acid within each of the identified epitope abolishes IgE binding (See abstract, page 18, Table 4, Table 5 and Table 6, in particular).

Yeung et al teach heated-killed bacteria such as listeria monocytogenes has innate adjuvant activity to provoke TH1 dominated immune response in treatment of allergy (see page 4146, col. 1, in particular). Yeung et al further teach heat-killed bacteria rather than live bacteria

are effective in reducing antigen/allergen specific IgE synthesis (see page 4151, col. 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the allergen in the live *E coli* in the pharmaceutical composition as taught by the '799 patent for the modified peanut allergens such as Ara h1, Ara h2, Ara h3 or a portion thereof that has a reduced ability to bind and crosslink IgE antibodies as taught by the WO 99/38978 publication and then heat-killed the *E coli* to rendered it dead and use it as a pharmaceutical composition to promote Th1-dominated immune response as taught by Yeung et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 99/38978 publication teaches the critical amino acids within each of the IgE binding epitope of the peanut protein such as Ara h1, Ara h2 and Ara h3 that are important for IgE binding and the modified peanut allergens are useful for a method of treating a subject susceptible to an anaphylactic reaction (allergic reaction) to peanut allergen (See abstract, in particular). It is within the purview of one ordinary skill in the immunology art to heat-killed microorganism such as *E coli* as a vaccine as taught by the '799 patent or (see col. 1, lie 52-57, in particular) and use the bacteria as an adjuvant as taught by Yeung et al.

9. Claims 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,888,799 (of record, March 1999, PTO 1449) in view of WO 99/38978 publication (of record, Aug 1999, PTO 1449) and Yeung et al (of record, J Immunology 161: 4146-4152, 1998; PTO 892) as applied to claims 34-43 above, and further in view of the US Pat No 6,270,723 (filed Oct 2, 1998; PTO 892) or Evans et al (of record, FEMS Microbil Immunol 1(3): 117-25, Dec 1998; PTO 892).

The combined teachings of the '799 patent, the WO 99/38978 publication and Yeung et al have been discussed supra.

The claimed invention in claim 44 differs from the teachings of the references only in that composition wherein the *E coli* was skilled by chemical treatment.

The claimed invention in claim 45 differs from the teachings of the references only in that composition wherein the *E coli* was skilled using a chemical selected from the group consisting of iodine, bleach, ozone, and alcohols.

The '723 patent teaches various methods such as heat (see col. 1, lines 15-30, col. 7, line 17-30, col. 11, line 66, in particular), chemical treatment such as alcohols (see col. 1, line 21, in particular), bleach (see col. 10, line 39-40, in particular) or pressure sterilization (ozone) to kill, or inactivate bacteria such as *E coli* (see col. 11, lines 42-67, col. 15, line 8, in particular). The '723 patent teaches these methods can improve the safety of vaccine or any product used by patient (see col. 8, lines 26-67, col. 9, lines 1-15, in particular).

Evans et al teach non-replicating dead *E coli* containing therein any desired antigen as a vaccine are efficient vehicle in terms of delivering antigens to the gut immune system (see abstract, in particular). Evans et al teach dead *E coli* can be obtained by treatment with chemical treatment such as Colicin E2 or heat treatment (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to kill any *E. coli* expressing modified allergen as taught by the '799 patent, the WO 99/38978 publication and Yeung et al by means of chemical treatment as taught by the '723 patent or Evans et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because a successful vaccine preparation method should ideally resulted in a high degree of bacteria inactivation while maintaining its ability to stimulate a protective immune response and these methods can improve the safety of vaccine or any product used by patient as taught by the '723 patent (see col. 8, lines 26-67, col. 9, lines 1-15, in particular). Evans et al teach non-replicating dead *E coli* containing therein any desired antigen as a vaccine are efficient vehicle in terms of delivering antigens to the gut immune system (see abstract, in particular).

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

13. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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